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PATHOGENESIS OF ACNE

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Summary The rate of sebum excretion was measured in individuals who had acne, who had had acne, or who had never had acne. In males over ten and females over fifteen with no present or past acne, sebum excretion increased until the third to fourth decade and then decreased, the rate of decrease being similar in both sexes. The rate of sebum excretion was greater in females aged ten to fifteen years than in males of the same age but was greater in all other age-groups in the males. The rate of sebum excretion in females was greater at age ten to fifteen years than at age sixteen to twenty; this contrasts with the findings in males. This can be explained if (1) the onset of puberty was earlier in females; (2) seborrhœa precedes clinical acne. Patients with acne had seborrhœa, and the severity of the clinical acne was directly related to the rate of sebum excretion. The sex difference in sebum secretion was less in patients with acne than in the controls without acne. In healthy individuals who had had acne there was a persistently increased rate of sebum excretion, and the difference in sebum-excretion rate between males and females was less striking than in the control population who had never had acne. It is concluded that acne is due to the interaction between an increased rate of sebum secretion and a second factor (increased resistance to sebum flow from organic obstruction or increased sebum viscosity). A rational experimental approach to the treatment of acne is therefore by reduction of sebum secretion by an antiandrogen or metabolic inhibitor, or by decreasing resistance to sebum flow (e.g., by reducing its viscosity).

Introduction

PATIENTS with acne have seborrhœa, but the precise relationship between acne and seborrhœa is unknown. We have investigated this by measuring the rate of sebum excretion in patients with acne or different grades of severity. We have also noticed that a middle-aged population who have had acne in their youth maintain a greasy skin although the acne has totally regressed. In view of the ætiological importance of this observation we measured sebum excretion in middle-aged men and women and related this to a previous history acne.

Materials and Methods

Method

Sebum secretion was measured by the method of Strauss and Pocchi (1961) modified by Cunliffe and Shuster (1969a). This method indirectly measures the rate of sebum secretion, and we prefer to call it by the descriptive term " rate of sebum excretion " (Cunliffe and Shuster 1969a).

Patients and Controls

350 subjects aged from ten to sixty-nine years were investigated in three groups:

(1) *No past or present acne.*—52 males and 87 females; none had acne or a history of physical signs of past acne. The criteria here were stringent—no patient was accepted with any sign of acne, however mild.

(2) *Adolescent acne.*—60 males and 100 females. The acne was divided clinically into four grades, grade 1 being the least severe and grade 4 the most severe.

(3) *Acne in the past.*—28 males and 23 females with a history of previous acne, and with signs such as follicular scarring. These patients had been completely free of acne for many years.

No subject was using topical or systemic therapy at the time of the investigation. Care was taken to prevent contamination of the collection papers with pus or serum which was present on the forehead of some of the patients with severe acne.

Results

No Past or Present Acne

Only 3 males aged between sixteen and twenty years had no sign of acne, and the results in the age-group ten to twenty years are therefore subdivided into two

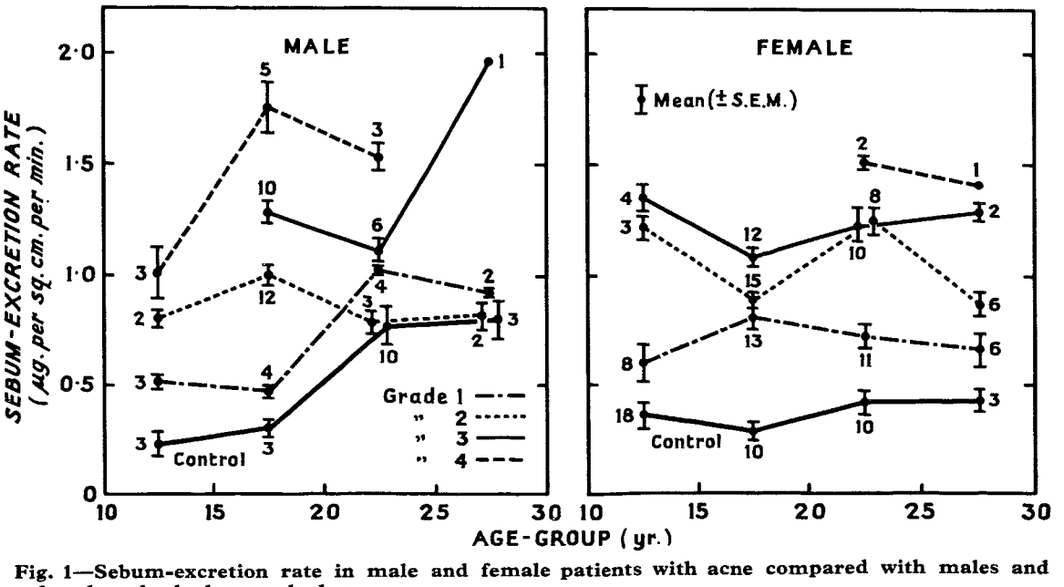

Fig. 1—Sebum-excretion rate in male and female patients with acne compared with males and females who had never had acne.

periods. Between ten and fifteen years the rate of excretion was greater in females than in males but at all other age-groups the rate of sebum excretion was much greater in males than in females. Another feature of the sebum excretion in puberty was the finding that the rate was greater in females aged ten to sixteen years than in females aged sixteen to twenty years. With this exception it increased in both males and females up to the third or fourth decade and then declined in both sexes. In absolute terms the decrease was no greater in females than in the males, but since the initial rate of excretion was greater in younger males the decrease with age was proportionately greater in the females.

Active Acne

The rate of sebum excretion for males and females in relation to the severity of the acne is shown in fig. 1. In both males and females the rate of sebum excretion was greater in patients with acne than in the controls, furthermore this increment was directly related to the severity of the acne (fig. 1). The sex difference in the rate of sebum excretion is less in patients with acne than in controls without acne.

Acne in the Past

The rate of sebum excretion in males and females who had had acne in the past is compared in fig. 2 with the controls who had never had acne. In both males and females of all ages studied there was a higher rate of sebum excretion in those who had had acne than in those who had not. Equally striking was the smaller difference between the sebum-excretion rates in males and females who had had acne as compared with the controls.

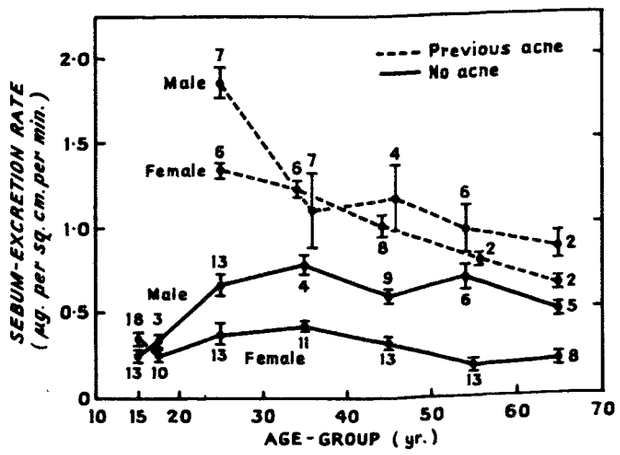

Fig. 2—Sebum-excretion rate in males and females without acne but who have had acne in the past compared with males and females who have never had acne.

Discussion

The method we used measures the rate of excretion of sebum to the skin surface. This is probably related to the pool of previously secreted sebum, and in interpreting the results it must be remembered that this is an indirect measurement of the rate of sebum secretion (Cunliffe and Shuster 1969a), other factors such as pool size and absorbability of sebum on to the collecting papers being constant.

We found that in healthy individuals who have never had acne, the rate of sebum excretion varies with age and sex. It is greater in females than in males aged ten to fifteen years but is greater in males thereafter. The secretory response of the sebaceous gland at puberty is dependent on androgen and a pituitary trophic hormone (Lasher et al. 1955). The greater rate of sebum excretion in females aged ten to fifteen years may, therefore, be due to the earlier onset of puberty and the greater increment in males after puberty could be due to sex differences in androgen secretion. We suspect that seborrhœa precedes clinical acne and that the sebum-excretion rate found in the healthy girls aged ten to fifteen years was unduly high due to the inclusion of girls with a pre-acne seborrhœa: the acne was clinically evident later and hence the rate of sebum excretion was less in healthy females without acne aged sixteen to twenty years. The precise mechanism of the sex differences in sebum secretion will require further studies, particularly in the younger age-group.

Our findings in relationship to age and sex differ from those of Strauss and Pocchi (1963) who found that the decrease in the rate of sebum excretion with age was greater in females than males. The probable reason for this lies in our observation of continued seborrhœa in middle-aged patients who had acne and in the higher incidence of acne in males. It follows that a randomly selected middle-aged population will contain more males with a previous history of acne and hence an increased rate of sebum excretion.

Our findings show that the severity of the acne and the degree of seborrhœa are directly related. This accords with the prevailing view that the rate of sebum secretion is a major causative factor in acne. A further observation of interest is that in those with a past history of acne the sex difference in the rate of sebum excretion was very much less than in healthy individuals who had never had acne. This observation could be explained by an increased secretion of a sebotrophic hormone, such as androgen, or an increased gland response to the trophic hormone. Alternatively, the role of sebotrophic hormones may be permissive, seborrhœa being transmitted as a genetic characteristic, the expression of which depends mainly on endocrine factors. This happens in male-pattern baldness, the tendency to which is transmitted as a simple dominant which is expressed only in the presence of adequate circulating androgen. We have some (unpublished) evidence for a similar mechanism in the seborrhœa of acne.

The persistent seborrhœa which we have found in healthy individuals who have had acne in the past raises some interesting problems, both in relationship to acne and to other aspects of sebaceous gland function. It is clear, for example, that any future study of sebaceous gland function in middle age must be related to a past history of acne: the discrepancy between our findings and those of Strauss and Pocchi (1963) are due to their failure to exclude those who had previously had acne from their middle-aged population, and the significance of seborrhœa in a group of middle-aged women with breast carcinoma (Strauss and Pocchi 1968) must also be reviewed in the light of these new observations (Burton, Cunliffe, and Shuster 1969).

We have found that acne occurs only in patients with a seborrhœa and that the severity of the acne is related to the degree of seborrhœa. Yet when the acne regresses after puberty it does so despite a persistent increase in the rate of sebum excretion. It is possible, moreover, to have a considerable seborrhœa without acne as in post-encephalitic parkinsonism and in acromegaly (Burton, Cunliffe, and Shuster 1969).

Acne cannot develop without an increased rate of sebum secretion but, since the seborrhœa persists after the acne

regresses, there must be a second factor (or factors) which can operate only in the active phase of the disease, usually puberty. In acne, unlike healthy skin, we have found many individual follicles do not deliver sebum to the skin surface (Shuster 1964, unpublished observations; Burton, Cunliffe, and Shuster 1969). This could be due to organic obstruction in the pilosebaceous follicles or to an increase in sebum viscosity. Resistance to sebum flow is probably the second factor and would lead directly to sebum retention, bacterial colonisation, and clinical acne.

From this analysis we conclude that procedures which lead to a reduction in the rate of sebum secretion will ameliorate acne. So far we have had no success with the antiandrogen cyproterone acetate (Cunliffe and Shuster 1969b) and nicotinacide, an inhibitor of lipid synthesis (Cunliffe and Shuster 1969c). Mitigation of the second factor by reducing the resistance to sebum flow, for example by decreasing sebum viscosity, would be an equally important approach to the treatment of acne.

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GENERALISED NON-PROGRESSIVE VACCINIA ASSOCIATED WITH IgM DEFICIENCY

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Summary 7 infants developed generalised non-progressive vaccinia after smallpox vaccination; they recovered completely on symptomatic therapy. Their serum IgM and IgA levels were significantly lower than those of a control population, and there was a proportionate diminution in isohæmagglutinin titre. Lymphocyte-counts were normal. 1 had normal lymphocyte transformation to phytohæmagglutinin, and there was no clinical evidence of gross cellular-immunity deficiency. It is suggested that the deficiency of the IgM antibody response may have caused the dissemination of vaccinia. The incidence points to a form of clinically significant immunity deficiency in about 1 per 1000 of the child population.

Introduction

PRIMARY vaccination is usually followed by an orderly and predictable sequence—formation of papule, vesicle, pustule, and crust, and extrusion of the scab, leaving a visible scar. The limitation of the extent of the lesion and the recovery from it depends, presumably, on specific immunity (cellular and humoral), interferon, and perhaps some other cellular factors, and so it is possible that deficiency or dysfunction of any of these factors might be associated with progression or dissemination of the lesion. The fatal syndrome of progressive necrotic vaccinia is associated with deficiency or abnormal function of lymphocytes, with or without defective antibody formation (Fulginiti et al. 1968), but most patients with hypogammaglobulinæmia react normally to vaccination (Medical Research Council Working-party 1969). Generalised non-progressive vaccinia is also a well-recognised syndrome (Downie 1959, Waddington et al. 1964, Neff et al. 1967) but it has not been correlated with any immunological abnormality. We describe here 7 patients with this syndrome; 5 of them had significantly low levels of IgM and IgA.

Clinical and Immunological Findings

7 infants, aged three to seven months, were seen at the All India Institute of Medical Sciences, New Delhi, during a period of twenty-four months; they had a second crop of lesions after primary smallpox vaccination, by the scratch technique, with freeze-dried vaccine lymph made in Russia. These metastatic lesions developed seven to twelve days after vaccination, over a period of forty-eight to ninety-six hours; the lesions numbered 20–50 and were mainly on the front and the back of the trunk. They followed the course, typical of primary vaccinia lesions and healed in three to four weeks; most of them left small thin scars. The primary lesion was slightly more severe than usual and took six to ten weeks to heal, leaving a puckered thick scar. No systemic symptoms were recorded. All the babies recovered completely on symptomatic therapy. Blood was collected for immunological tests two to eight days after the development of the diffuse rash and, in 1, eighteen months later. Blood was also collected from seven children from the same community, matched as closely as possible for age and sex (table I), who had reacted normally to vaccination. Serum-levels of immunoglobulins (table I, fig. 1) were determined by the single-gel diffusion method (Mancini et al. 1965). Results are expressed as % of Medical Research Council provisional standard serum. The difference between log values for each pair was calculated, and the range of these differences was significantly different from zero for IgM (mean 0·61, S.D. 0·43; $t=3·47$; $0·02>P>0·01$) and IgA (mean 0·61, S.D. 0·60; $t=2·46$; $0·05>P>0·02$) but not for IgG (mean 0·08, S.D. 0·30; $t=0·64$; $P>0·1$), though two of them had values comparable with

TABLE I—SERUM-IMMUNOGLOBULINS, ISOHÆMAGGLUTININ TITRES, AND LYMPHOCYTE-COUNTS

Age (mo.)	Sex	Serum-immunoglobulins (% standard)			Reciprocal iso-hæmagglutinin titres		Lympho-cytes (c.mm.)
		IgG	IgA	IgM	α	β	
Patients:							
3	M	172	<2·5	8	0	0	3078
4	M	160	4	12	0	0	3556
4	F	480	312	108	..	..	3045
5	F	128	16	20	1	2	3450
6	F	232	132	368	128	2	2499
6	M	84	60	64	2	8	3034
7	M	92	52	64	4	4	4028
Controls:							
3	F	108	100	168	4	0	3500
4	M	200	172	132	128	128	3680
4	M	84	132	128	8	16	4580
5	F	160	80	200	..	..	3200
6	F	100	200	180	128	128	2650
6	M	176	152	284	8	0	2800
7	M	160	80	200	16	0	2100

Patient and control series are arranged in the order of pairing for the statistical analysis.